Cognitive outcome of early school-aged children born very preterm is not predicted by early short-term amplitude-integrated electroencephalography

Feldmann, Maria ; Rousson, Valentin ; Nguyen, Thi Dao ; Bernet, Vera ; Hagmann, Cornelia ; Latal, Beatrice ; Natalucci, Giancarlo

Abstract: AIM We investigated the association between early amplitude-integrated electroencephalography (aEEG) and cognitive outcome in very preterm infants at early school-age. METHODS This prospective cohort study, conducted in the Department of Neonatology, University Hospital Zurich, Switzerland, from 2009-2012, comprised infants born at less than 32 weeks of gestation, who underwent continuous aEEG recording during the first four days of life. Cognitive outcome was assessed with the Kaufman-Assessment Battery for Children at five years. Univariate and multivariate logistic regressions were calculated between aEEG parameters and normal cognitive outcome, defined as an intelligence quotient (IQ) of at least 85. RESULTS The 118 (52.5% male) infants were born at a mean gestational age of 29.9 weeks and a mean birth weight of 1,235 ±363 grams. We followed up 89 children at the age of five and they had a mean IQ of 97.8 ±12.7 with 21.3% under 85 - and 2.2% had cerebral palsy. Univariate analyses found associations between aEEG measures and normal cognitive outcome, but these were no longer significant after adjustment for confounders. Socioeconomic status and neonatal morbidity were independent predictors of cognitive outcome. CONCLUSION Early short-term aEEG did not predict later cognitive outcome in our cohort of very preterm infants.

DOI: https://doi.org/10.1111/apa.14919

DR. MARIA FELDMANN (Orcid ID : 0000-0002-6616-3510)

Article type : Regular Article

Cognitive outcome of early school-aged children born very preterm is not predicted by early short-term amplitude-integrated electroencephalography

Short title

Predictive value of amplitude-integrated electroencephalography

Authors

Maria Feldmann[1,2], Valentin Rousson[3], Thi Dao Nguyen[4], Vera Bernet[5], Cornelia Hagmann[2,5], Beatrice Latal[1,2], Giancarlo Natalucci[1,4]

Corresponding Author

Giancarlo Natalucci, UniversitätsSpital Zürich, Klinik für Neonatologie, Frauenklinikstrasse 10, 8091 Zürich, Giancarlo.Natalucci@usz.ch, Tel. +41 44 255 53 45

Affiliations

[1]Child Development Centre, University Children's Hospital Zurich, Switzerland
[2]Children's Research Centre, University Children's Hospital Zurich, Zurich, Switzerland
[3]Institute for Social and Preventive Medicine, Statistical Unit, Lausanne University Hospital, Lausanne, Switzerland
[4]Department of Neonatology, University of Zurich and University Hospital Zurich, Switzerland
[5]Department of Neonatology and Paediatric Intensive care, University Children's Hospital Zurich, Switzerland

Abstract

Aim

We investigated the association between early amplitude-integrated electroencephalography (aEEG) and cognitive outcome in very preterm infants at early school-age.

Methods

This prospective cohort study, conducted in the Department of Neonatology, University Hospital Zurich, Switzerland, from 2009-2012, comprised infants born at less than 32 weeks of gestation, who underwent continuous aEEG recording during the first four days of life. Cognitive outcome was assessed with the Kaufman-Assessment Battery for Children at five years. Univariate and

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apa.14919

multivariate logistic regressions were calculated between aEEG parameters and normal cognitive outcome, defined as an intelligence quotient (IQ) of at least 85.

Results

The 118 (52.5% male) infants were born at a mean gestational age of 29.9 weeks and a mean birth weight of 1,235 ±363 grams. We followed up 89 children at the age of five and they had a mean IQ of 97.8 ±12.7 with 21.3% under 85 – and 2.2% had cerebral palsy. Univariate analyses found associations between aEEG measures and normal cognitive outcome, but these were no longer significant after adjustment for confounders. Socioeconomic status and neonatal morbidity were independent predictors of cognitive outcome.

Conclusion

Early short-term aEEG did not predict later cognitive outcome in our cohort of very preterm infants.

Key words

amplitude-integrated electroencephalography, cognitive outcome, prediction, preterm infant, socioeconomic status

Key notes

- We investigated the association between early amplitude-integrated electroencephalography (aEEG) and cognitive outcome in 89 very preterm infants when they were five years of age.
- Univariate logistic regression analyses found associations between aEEG measures and normal cognitive outcomes, but these were no longer significant after adjustment for confounders.
- Early short-term aEEG did not predict later cognitive outcome in our cohort of very preterm infants born at a mean gestational age of 29.9 weeks.

INTRODUCTION

Preterm born infants are at high risk for cognitive impairment in childhood and adolescence (1). During the intermediate postnatal period, very preterm infants are particularly vulnerable to brain lesions and other non-neurological complications. Amplitude-integrated electroencephalography (aEEG) has been proven to be a valuable tool for cerebral function monitoring and allows for detection of background pattern deteriorations due to brain injury and subclinical seizures (2). The simplified set up and interpretability of aEEG enables continuous neuromonitoring, and thus allows the intensive care team to immediately respond to changes in cerebral functioning (2). Beyond the guidance for clinical decision making, aEEG background pattern serves as an indicator of cerebral functional (3,4), and structural (5) maturation. In other at risk populations, such as infants with hypoxic ischemic encephalopathy, aEEG background pattern is one of the most powerful predictors of neurodevelopmental outcome (6). A similar association has been found in neonates after open

heart surgery (7), in which background pattern and ictal discharges on aEEG furthermore helped to detect brain lesions (8).

In the preterm population, neonatal aEEG metrics, such as cycling, background pattern, maturity score and seizure activity, have been associated with neurodevelopmental outcome up to three years of age (9-14). However, there is a significant heterogeneity in studies that results from a broad variety of assessed aEEG parameters and outcome measurements, as systematically reviewed by Fogtmann et al (15). Additionally, whereas several studies focused on the predictive value for early childhood outcome, information on the association of early aEEG with neurodevelopmental outcome at school-age is scarce (16). Thus, to date, aEEG has not been broadly implemented into standard clinical neuromonitoring of preterm infants.

Hence, the aim of the present study was to assess the association of early aEEG recorded during the first four days of life, and the trajectory of aEEG characteristics between day one and four with cognitive outcome at five years of age in very preterm infants.

METHODS

Study population

This prospective cohort study was conducted in the Department of Neonatology of the University Hospital Zurich, Switzerland between January 2009 and February 2012. Inborn preterm infants with a gestational age of less than 32 weeks were included. Patients with congenital anomalies, central nervous system infections or metabolic disorders were excluded. Gestational age was assigned based on the best obstetrical estimate according to last menstrual cycle and first trimester ultrasound if available. Cranial ultrasound was performed at day one, three and seven of life and repeated weekly until hospital discharge. Mild brain lesions were defined as intraventricular haemorrhage grade I–II and, or periventricular leukomalacia grade I, whereas severe brain lesions were defined as grade III intraventricular haemorrhage and periventricular haemorrhagic infarction, cerebellar haemorrhage, cerebral atrophy and cystic periventricular leukomalacia as described previously (17). Socioeconomic status was assessed based on maternal education and paternal occupation and was scored according to Largo et al (18). Scores were transformed so that higher scores indicate higher socioeconomic status, ranging from 2 to 12. Perinatal characteristics and type of sedation during aEEG recording were prospectively noted.

aEEG assessment

Cerebral functional monitoring was carried out with a two-channel Brainz BRM3 aEEG monitor (Natus Newborn Care, California, USA) and recorded with bi-parietal hydrogel electrodes, corresponding to C3 and P3, and C4 and P4 of the international electroencephalogram classification 10–20 system with a ground F_Z placed on the right or left shoulder (19). The aEEG was obtained by amplification and filtering of the raw EEG and attenuation of the activity at < 2Hz and > 15Hz was performed. The amplitudes were integrated semi-logarithmically, rectified and time compressed (1 h/6 cm of recording display scale). Continuous aEEG recording was conducted from the first to the fourth day of life. aEEG pattern analysis was performed on three-hour periods of cross-cerebral P3-P4 aEEG recordings with impedance below 12 kΩ. Tracing periods with either suspected seizure activity or artefacts were excluded from the analysis as described elsewhere (5).

Visual and quantitative aEEG analysis

To semi-quantitatively analyse the aEEG patterns two scoring systems were applied. Brain maturation was assessed by the maturity score established by Burdjalov et al (4). The score is composed of four component variables (continuity, cycling, amplitude of lower boarder and bandwidth) that sum up in a total maturity score ranging from 0–13 with increasing score indicating more mature brain activity. The cycling component was furthermore separately considered as cycling sub-score with scores ranging from 0–5 and increasing with cycling activity (4). The background pattern was evaluated according to the classification that was introduced by Hellstrom-Westas and Rosen (20): zero was inactive, flat, one was low voltage, two was burst-suppression, three was discontinuous and four was continuous. Semi-quantitative aEEG parameters were averaged for the whole recording period from day one to day four. A minimum of two measurements to determine the averages was required. Quantitative analysis of the aEEG tracings was automatically performed using BrainZ Analyze Research software, version 1.71 (Liggins Institute, Auckland, New Zealand). Raw aEEG data was exported and one-minute average values of the maximum and minimum amplitudes were calculated for each period. To analyse the association between quantitative aEEG measures and cognitive outcome, measurements were averaged for the whole recording period. Only a single measurement was required, since aEEG minimum and maximum amplitude parameters were already averaged values. To investigate the trajectory of aEEG parameters during the first four days of life the slopes were calculated from a minimum of three measurements. Cohen's kappa for inter-rater agreement between the two aEEG raters (GN, CH) blinded to the neonatal course was 0.79 (95% CI 0.75; 0.82) for the total maturity score and 0.60 (95% CI 0.52; 0.66) for the cycling sub-score, respectively. For statistical analysis one rater's aEEG scores (GN) were considered.

Neurocognitive assessment at five years of age

Cognitive outcome at five years of age was assessed with the first and second editions (21) of the German version of the Kaufman Assessment Battery by experienced developmental paediatricians at the Child Development Centre at the University Children's Hospital Zurich. The mental processing composite scale of the First Edition and the mental processing index of the Second Edition were considered equivalent to an intelligence quotient (IQ) with a mean (SD) value of 100 ±15, as a general measure of cognitive ability. An IQ of at least 85 was considered as normal. According to the International Classification of Diseases 10th Revision of the World Health Organisation, an IQ below 85 is more than one SD below the mean and defines the cut-off for borderline intellectual functioning, and an IQ below 70 defines the range of intellectual disability. In this study, we will refer to the complete range of IQ below 85 as unfavourable cognitive outcome. Additionally, each child underwent a standardised neurological examination. Cerebral palsy was defined according to Rosenbaum et al (22).

Statistical analysis

Descriptive statistics for continuous variables were reported as median and interquartile range (IQR) as they were non-normally distributed. Merely weight at birth was normally distributed and accordingly reported as mean and standard deviation (SD). Proportions were reported for categorical variables. Unadjusted and adjusted logistic regression models were calculated to

evaluate the association between either the average or the trajectory of aEEG parameters during the first four days of life with normal cognitive outcome, i.e. IQ equal or above 85, at five years of age. The trajectory of an aEEG parameter was summarised by the slope of a regression line calculated separately for each individual. In the adjusted model, perinatal characteristics known to influence outcome were considered as potential confounders: gestational age, male sex, administration of morphine for sedation during aEEG monitoring and small for gestational age with a birth weight below the 10 percentile. Furthermore, socioeconomic status has been included as covariate due to its well documented influence on neurodevelopmental outcome (18). In the logistic regression models, for the sake of comparison and without affecting any p-value, aEEG parameters were standardised, such that the provided odds ratios (OR) refer to an increase of one standard deviation whatever the aEEG parameter considered. Missing values in socioeconomic status were identified in 11% of the datasets and imputed by means of multiple imputation using the *MICE* (Multivariate Imputation by Chained Equations) package implemented in R (R Foundation for Statistical Computing, Vienna, Austria) (23). The Predictive Mean Matching method was used to generate 100 imputed datasets, which were then combined using the *pool()* function. The covariates of the logistic regression analysis, such as gestational age, sex, sedation, small for gestational age, and the cognitive outcome were included as predictors to impute the missing socioeconomic status values. P values of < 0.05 were considered statistically significant. All analyses were performed using R version 3.4.2.

Ethics

The institutional ethics boards of the Canton of Zurich (KEK ZH StV-35/08) approved the study protocol. Written, informed consent was obtained from the parents or primary caretakers.

RESULTS

Study population

Continuous aEEG recording was performed in 120 preterm infants, but two infants had to be excluded due to a later diagnosis of leukaemia in one and a diagnosis of a genetic syndrome in the other. The majority of the cohort were male (52.5%), they had a median (IQR) gestational age of 29.9 weeks (28.2, 30.9) and a mean birth weight of 1,235 ±363g. aEEG tracings of all infants were evaluated. The aEEG recording began at a median age of 18 (IQR 12, 21) hours and was continuously performed until 87 (IQR 81, 96) hours after birth. Cranial ultrasound was mildly abnormal in 20/118 infants (16.9%) and severely abnormal in 7/118 infants (5.9%).

Neurocognitive outcome at five years of age

Neurocognitive follow-up at five years was performed in 89 of 118 infants. Of the remaining 29, four died and another 25 were lost to follow-up. Thus, the follow-up rate of the surviving infants was 78.1%. Median corrected age at follow up was 68.6 months (IQR 65.5, 71.2). Perinatal characteristics of the study participants that underwent follow up are displayed in Table 1, stratified by their five-year cognitive outcome with IQ equal or above 85. Baseline characteristics differed between infants with and without follow up. Subjects that were lost to follow up had a significantly higher gestational age (31.0 versus 29.6 weeks) and birth weight (1,390.8 versus 1,1213.3 g) than those who were

assessed at five years (Table S1). Follow up assessment at five years revealed a mean (SD) IQ of 97.8 (12.7) ranging from 65 to 121. IQ below 85 occurred in 21.3%, whereas cerebral palsy was found in 2.2%.

aEEG measures in infants with normal versus unfavourable cognitive outcome

Neonates with unfavourable cognitive outcome at five years of age had lower median scores for aEEG background pattern, total maturity score and cycling sub-score than neonates with normal cognitive outcome. Of the quantitative parameters, the mean minimum aEEG amplitude, and the mean maximum aEEG amplitude, were lower in infants with unfavourable compared to normal cognitive outcome when averaged over the four days of recording period (Table 2)**.**

Prediction of outcome by aEEG measures

In univariate logistic regression analyses we found that higher total maturity scores, cycling sub-scores, and more mature background pattern and a higher minimum aEEG amplitude were associated with increased odds of normal cognitive outcome at five years of age. After adjusting for the confounders gestational age, sex, sedation, small for gestational age and socioeconomic status none of the associations remained significant (Table 2, Figure 1). The results of the adjusted logistic regression models showed that each unit increase of socioeconomic status was associated with a 40% increase in the odds of having an IQ equal or above 85. These results were not altered by multiple imputation of missing values on socioeconomic status, since very similar results were obtained when including only those children without missing socioeconomic status in our analysis. Furthermore, morphine sedation during aEEG monitoring was associated with a decrease in the odds of having a normal cognitive outcome with ORs ranging from 0.1–0.2. This indicates that the odds of having an IQ equal or above 85 was 5–10 times lower for children that required sedation during the first four days of life. When comparing perinatal clinical characteristics of sedated versus non-sedated neonates, we found that sedated neonates had a lower gestational age (27.6 versus 30.0 weeks), birth weight (1029.4 versus 1271.6 g) and a higher Score for Neonatal Acute Physiology with Perinatal Extension-II (24) compared to non-sedated neonates (21.5 versus 18) (Table S3).

Prediction of outcome by aEEG trajectories

We also examined whether the trajectories of aEEG, quantified as the slope of aEEG characteristics over the four-day recording period, were associated with cognitive outcome. No association was found in univariate and multiple logistic regression models with cognitive outcome at five years of age (Table 3).

DISCUSSION

This prospective cohort study investigated the predictive value of early short-term quantitative and semi-quantitative aEEG parameters for cognitive outcome at school-age in very preterm born infants. We hypothesised that aEEG is associated with IQ at five years of age. Although we found evidence for univariate associations of early aEEG parameters during the first four days of life with cognitive outcome, these associations did not remain after adjustment for confounders. In multiple logistic regression models, we found that higher socioeconomic status was independently associated

with higher odds of having a normal IQ at five years of age. Furthermore, we found that morphine sedation was associated with a decrease in the odds of having an IQ within the normal range.

Despite previous reports of the predictive value of early aEEG recordings for neurodevelopmental outcome up to three years of age, we were not able to confirm the association for cognitive outcome at five years of age. This might be due to substantial differences in the assessment and analysis methods of aEEG recordings, analysed aEEG time points, outcome measurements, and compositions of combined outcomes. In line with our aEEG assessment methods Huning et al (25) used the total maturity score by Burdjalov et al (4) and the background pattern assessment by Hellstrom-Westas et al (2), whereas others applied different aEEG background scoring systems (26) and quantitative analysis methods such as interburst intervals (11), and dichotomised aEEG tracings into normal and abnormal (12) patterns. This substantial variability in aEEG analysis methods hampers the comparability among studies, and with our results. However, the aim of this study was to assess whether early aEEG recordings could inform prognosis in very preterm infants in a clinically applicable way. Thus, the ease of the assessment was taken into account when choosing the aEEG parameters and time points—here the average over four days—for this study. Furthermore, the absence or sparse correction for confounders applied in other studies (11) might explain the differences in results. In line with this, we found a univariate association between the assessed aEEG parameters with neurocognitive outcome at five years of age, but found it to be confounded by neonatal clinical and demographic covariates such as socioeconomic status and sedation. The present findings conform to the recent report of Middel et al (16) who observed only weak evidence for an association between presence of early cyclicity in aEEG and IQ in preterm infants at early school-age.

When correcting for confounders, we found that higher socioeconomic status was independently associated with higher odds of having a normal IQ at five years of age. We chose to correct for socioeconomic status, since it has been demonstrated by others to be a strong predictor of developmental trajectories in preterm born infants (18). The present study results underline the importance of taking socioeconomic status into account, when analysing prediction of biomarkers for intellectual outcome in newborn infants at high neurodevelopmental risk, particularly on the long-term. Furthermore, in this cohort morphine sedation during aEEG monitoring was found to be associated with a decrease in the odds of having an IQ within the normal range. These results are in line with previous studies reporting that morphine administration in preterm born infants may affect aEEG tracings (17), and may be associated with adverse neurodevelopmental outcome, and reduced regional cerebral growth (27). However, post hoc analyses of baseline characteristics among neonates who received morphine sedation during aEEG recording in this cohort, compared to non-sedated neonates revealed some collinearity of morphine sedation and other variables, such as lower gestational age, higher Score for Neonatal Acute Physiology with Perinatal Extension-II. This indicates a high clinical instability of the sedated subjects. Hence, suggesting that sedation in the present cohort is rather a surrogate marker for unfavourable clinical course, which in turn impacts later adverse neurodevelopmental outcome. As we did not collect data on cumulative dose of morphine administration during the neonatal period, we are not able to analyse any further association between neonatal morphine exposure and neurodevelopment, as already reported for instance by Zwicker et al (27).

The early time-point, and the brevity of the monitoring period might give another explanation for the absence of a predictive value of early aEEG with five-year outcome in the present cohort. Relevant neonatal morbidities might occur later than during the first week of life and are not mirrored by early aEEG background pattern deteriorations. Among them, some clinical complications such as necrotising enterocolitis, bronchopulmonary dysplasia, or sepsis have a well-described impact on neurodevelopmental outcome (28). The complexity of outcome prediction might be even more pronounced for school-age compared to early infancy outcome, and could explain the differing results of this study and previous reports. In that sense, longitudinal aEEG recording during the neonatal course up to term equivalent age might be more informative in terms of long term prognosis of neurodevelopmental outcome, as demonstrated by others (12,29). In the comparison of baseline characteristics, children that were lost to follow up were found to be born less premature and with higher birth weight than children that underwent follow up. It may be speculated, that the inclusion of children lost to follow up could have further reduced the proportion of unfavourable outcome in the whole cohort, and thus the likelihood of finding an association of early aEEG measures with cognitive performance. This further supports our finding, that early aEEG is not predictive of cognitive outcome at five years of age.

This study has some limitations that need to be mentioned. The study presents the predictive value of early aEEG in a cohort with favourable outcome. Mean IQ in this cohort was within the normal range, however IQ below 85 and cerebral palsy occurred at a higher rate than in the normal population. Nonetheless, it is possible that the power to find an association of aEEG with outcome was compromised by the low prevalence of unfavourable cognitive outcome in this cohort. Yet, although intellectual outcome in the present cohort was predominantly favourable, it is in line with results from previous studies as systematically reviewed by Brydges (1). Other factors that might have compromised the statistical power of our analysis might have been the small sample size and relatively high number of predictors that were included in the statistical models to control for confounding. We investigated the association of semi-quantitative and qualitative aEEG analyses methods with cognitive outcome at five years of age and did not assess other event-based quantitative aEEG analysis approaches, such as spontaneous activity transients frequency and length of interburst intervals, that have been shown by others to be associated with brain growth (30), and might thus be predictive of outcome. Brain injury was rare in this cohort, thus analyses of the predictive value of aEEG in subgroups according to brain injury severity was not possible.

CONCLUSION

In this prospective cohort study, we found a univariate association between early semi-quantitative and quantitative aEEG measures and cognitive outcome at early school-age in very preterm born children. However, socioeconomic factors and neonatal morbidity were stronger predictors of long-term cognitive outcome than early aEEG measures.

AKNOWLEDGMENTS

We gratefully thank all children and their parents who participated in this study.

ABBREVIATIONS

aEEG, amplitude-integrated electroencephalography;

IQ, intelligence quotient;

IQR, interquartile range;

OR, odds ratio;

SD, standard deviation.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

This study received financial support by the Swiss National Science Foundation (grant 33CM30-124101).

Figure 1: Univariate and multivariate logistic regression models of semi-quantitative (upper panel) and quantitative aEEG parameters (lower panel) and normal cognitive outcome at five years of age. Blue unadjusted model. Red adjusted for gestational age, socioeconomic status, sex, morphine sedation during aEEG and small for gestational age. Unadj, unadjusted; Adj, adjusted.

REFERENCES

1. Brydges CR, Landes JK, Reid CL, Campbell C, French N, Anderson M. Cognitive outcomes in children and adolescents born very preterm: a meta-analysis. *Dev Med Child Neurol* 2018; 60 5:452-68.
2. Hellstrom-Westas L, Rosen I, de Vries LS, Greisen G. Amplitude-integrated EEG Classification and Interpretation in Preterm and Term Infants. *NeoReviews* 2006; 7 2:e76-e87.
3. Klebermass K, Kuhle S, Olischar M, Rucklinger E, Pollak A, Weninger M. Intra- and extrauterine maturation of amplitude-integrated electroencephalographic activity in preterm infants younger than 30 weeks of gestation. *Biol Neonate* 2006; 89 2:120-5.
4. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. *Pediatrics* 2003; 112 4:855-61.

5. Natalucci G, Leuchter RH, Bucher HU, Latal B, Koller B, Huppi PS, et al. Functional brain maturation assessed during early life correlates with anatomical brain maturation at term-equivalent age in preterm infants. *Pediatr Res* 2013; 74 1:68-74.
6. Skranes JH, Lohaugen G, Schumacher EM, Osredkar D, Server A, Cowan FM, et al. Amplitude-Integrated Electroencephalography Improves the Identification of Infants with Encephalopathy for Therapeutic Hypothermia and Predicts Neurodevelopmental Outcomes at 2 Years of Age. *J Pediatr* 2017; 187:34-42.
7. Latal B, Wohlrab G, Brotschi B, Beck I, Knirsch W, Bernet V. Postoperative Amplitude-Integrated Electroencephalography Predicts Four-Year Neurodevelopmental Outcome in Children with Complex Congenital Heart Disease. *J Pediatr* 2016; 178:55-60 e1.
8. Claessens NHP, Noorlag L, Weeke LC, Toet MC, Breur J, Algra SO, et al. Amplitude-Integrated Electroencephalography for Early Recognition of Brain Injury in Neonates with Critical Congenital Heart Disease. *J Pediatr* 2018; 202:199-205 e1.
9. Jiang CM, Yang YH, Chen LQ, Shuai XH, Lu H, Xiang JH, et al. Early amplitude-integrated EEG monitoring 6 h after birth predicts long-term neurodevelopment of asphyxiated late preterm infants. *Eur J Pediatr* 2015; 174 8:1043-52.
10. Hellstrom-Westas L, Rosen I, Svenningsen NW. Cerebral function monitoring during the first week of life in extremely small low birthweight (ESLBW) infants. *Neuropediatrics* 1991; 22 1:27-32.
11. Wikstrom S, Pupp IH, Rosen I, Norman E, Fellman V, Ley D, et al. Early single-channel aEEG/EEG predicts outcome in very preterm infants. *Acta Paediatr* 2012; 101 7:719-26.
12. Klebermass K, Olischar M, Waldhoer T, Fuiko R, Pollak A, Weninger M. Amplitude-integrated EEG pattern predicts further outcome in preterm infants. *Pediatr Res* 2011; 70 1:102-8.
13. Kidokoro H, Kubota T, Hayashi N, Hayakawa M, Takemoto K, Kato Y, et al. Absent cyclicity on aEEG within the first 24 h is associated with brain damage in preterm infants. *Neuropediatrics* 2010; 41 6:241-5.
14. Bowen JR, Paradisis M, Shah D. Decreased aEEG continuity and baseline variability in the first 48 hours of life associated with poor short-term outcome in neonates born before 29 weeks gestation. *Pediatr Res* 2010; 67 5:538-44.
15. Fogtmann EP, Plomgaard AM, Greisen G, Gluud C. Prognostic Accuracy of Electroencephalograms in Preterm Infants: A Systematic Review. *Pediatrics* 2017; 139 2:e20161951.
16. Middel RG, Brandenbarg N, Van Braeckel K, Bos AF, Ter Horst HJ. The Predictive Value of Amplitude-Integrated Electroencephalography in Preterm Infants for IQ and Other Neuropsychological Outcomes at Early School Age. *Neonatology* 2018; 113 4:287-95.

17. Natalucci G, Hagmann C, Bernet V, Bucher HU, Rousson V, Latal B. Impact of perinatal factors on continuous early monitoring of brain electrocortical activity in very preterm newborns by amplitude-integrated EEG. *Pediatr Res* 2014; 75 6:774-80.
18. Largo RH, Pfister D, Molinari L, Kundu S, Lipp A, Duc G. Significance of prenatal, perinatal and postnatal factors in the development of AGA preterm infants at five to seven years. *Dev Med Child Neurol* 1989; 31 4:440-56.
19. van Rooij LG, de Vries LS, Handryastuti S, Hawani D, Groenendaal F, van Huffelen AC, et al. Neurodevelopmental outcome in term infants with status epilepticus detected with amplitude-integrated electroencephalography. *Pediatrics* 2007; 120 2:e354-63.
20. Hellstrom-Westas L, Rosen I. Continuous brain-function monitoring: state of the art in clinical practice. *Semin Fetal Neonatal Med* 2006; 11 6:503-11.
21. Kaufmann AS, Kaufmann NL. Kaufman Assessment Battery for Children—second edition (K-ABC-II): *Circle Pines, MN: American Guidance Service*, 2004.
22. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007; 109:8-14.
23. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2017
24. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *J Pediatr* 2001; 138 1:92-100.
25. Huning B, Storbeck T, Bruns N, Dransfeld F, Hobrecht J, Karpienski J, et al. Relationship between brain function (aEEG) and brain structure (MRI) and their predictive value for neurodevelopmental outcome of preterm infants. *Eur J Pediatr* 2018; 177 8:1181-9.
26. Olischar M, Klebermass K, Waldhoer T, Pollak A, Weninger M. Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. *Acta Paediatr* 2007; 96 12:1743-50.
27. Zwicker JG, Miller SP, Grunau RE, Chau V, Brant R, Studholme C, et al. Smaller Cerebellar Growth and Poorer Neurodevelopmental Outcomes in Very Preterm Infants Exposed to Neonatal Morphine. *J Pediatr* 2016; 172:81-7 e2.
28. Schlapbach LJ, Adams M, Proietti E, Aebischer M, Grunt S, Borradori-Tolsa C, et al. Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. *BMC Pediatr* 2012; 12 1:198.
29. El Ters NM, Vesoulis ZA, Liao SM, Smyser CD, Mathur AM. Term-equivalent functional brain maturational measures predict neurodevelopmental outcomes in premature infants. *Early Hum Dev* 2018; 119:68-72.
30. Benders MJ, Palmu K, Menache C, Borradori-Tolsa C, Lazeyras F, Sizonenko S, et al. Early Brain Activity Relates to Subsequent Brain Growth in Premature Infants. *Cereb Cortex* 2015; 25 9:3014-24.

TABLES

Table 1. Perinatal characteristic of the study infants stratified by cognitive outcome.

Perinatal variable	**Cognitive outcome**	
	normal	**unfavourable**
	n = 70	***n = 19***
Gestational age (weeks), median [IQR]	29.7 [28.6, 30.7]	29.0 [26.9, 29.9]
Birth weight (g), mean (SD)	1267.4 (369.4)	1013.7 (250.2)
Small for gestational age, n (%)	11 (15.7)	3 (15.8)
Male sex, n (%)	34 (48.6)	11 (57.9)
Preeclampsia, n (%)	16 (22.9)	3 (15.8)
Chorioamnionitis, n (%)	15 (21.4)	4 (21.1)
Caesarean section, n (%)	62 (88.6)	17 (89.5)
Arterial cord pH, median [IQR]	7.3 [7.3, 7.4]	7.3 [7.2, 7.4]
5-min Apgar, median [IQR]	7.5 [6.0, 9.0]	6.0 [6.0, 8.0]
SNAPPE-II, mean (SD)	19.7 (17.0)	27.3 (19.0)
Antenatal steroids, n (%)	52 (75.4)	14 (77.8)
Surfactant, n (%)	18 (26.1)	11 (61.1)
Respiratory distress, n (%)	65 (92.9)	18 (94.7)
Days on ventilation, median [IQR]	0.0 [0.0, 1.0]	2.0 [1.0, 6.0]
Major brain lesions, n (%)	2 (2.9)	1 (5.3)
Caffeine during aEEG, n (%)	15 (21.4)	8 (42.1)
Indomethacin during aEEG, n (%)	19 (27.1)	8 (42.1)
Morphine during aEEG, n (%)	6 (8.6)	7 (36.8)
SES, median [IQR]	9.0 [8.0, 12.0]	8.0 [5.8, 8.2]

IQR, interquartile range; SD, standard deviation; Small for gestational age, birth weight < 10 percentile; SNAPPE-II, Score for Neonatal Acute Physiology with Perinatal Extension-II; SES, socioeconomic status; CP, cerebral palsy.

Table 2: aEEG measures stratified by cognitive outcome and unadjusted and adjusted associations between aEEG measures and normal cognitive outcome at five years of age.

aEEG Parameter	Cognitive outcome		Unadjusted OR	95% CI	*p*	*Adjusted OR*	*95% CI*	*p*
	normal	**unfavourable**						
Maturity score, median [IQR]	6.0 [3.5, 8.5]	3.8 [2.0, 6.4]	1.91	(1.09; 3.36)	**0.024**	0.91	(0.36; 2.31)	0.84
Cycling sub-score, median [IQR]	1.3 [0.5, 2.2]	0.7 [0.0, 1.4]	1.83	(1.01; 3.33)	**0.047**	0.85	(0.34; 2.14)	0.73
Background pattern, median [IQR]	3.4 [3.0, 3.9]	2.8 [2.4, 3.6]	2.39	(1.38; 4.13)	**0.002**	1.7	(0.74; 3.91)	0.21
Min amplitude, mean (SD)	5.3 (1.0)	4.7 (1.4)	1.78	(1.03; 3.05)	**0.037**	1.04	(0.47; 2.29)	0.93
Max amplitude, mean (SD)	13.1 (2.5)	12.0 (3.9)	1.34	(0.79; 2.27)	0.27	0.92	(0.48; 1.76)	0.81

Associations were calculated with multiple logistic regression models adjusted for gestational age, sex, sedation, small for gestational age and socioeconomic status. Results are displayed as odds ratios (OR), 95% Confidence Interval (CI) and p-value. For results of covariates refer to Supplementary Table S2.

Table 3: Unadjusted and adjusted associations between slopes of trajectories of aEEG measures and cognitive outcome at five years of age.

aEEG Parameter Slopes	OR	95% CI	*p*
Maturity score			
unadjusted	1.87	(0.79; 4.46)	0.16
adjusted	1.33	(0.52; 3.4)	0.55
Cycling sub-score			
unadjusted	1.77	(0.87; 3.6)	0.12
adjusted	1.14	(0.49; 2.65)	0.76
Background pattern			
unadjusted	0.97	(0.57; 1.65)	0.90
adjusted	0.92	(0.51; 1.67)	0.79
Min amplitude			
unadjusted	1.19	(0.65; 2.17)	0.58
adjusted	1.15	(0.54; 2.49)	0.72
Max amplitude			
unadjusted	0.83	(0.49; 1.39)	0.47
adjusted	0.85	(0.45; 1.63)	0.63

Association were calculated with multiple logistic regression models adjusted for gestational age, sex, sedation, small for gestational age and socioeconomic status. Results are displayed as odds ratios (OR), 95% Confidence Interval (CI) and p-value.